Remarks

Status of the Claims and Support for the Amendments

Claims 1, 14, 52, 53, 57, 60 and 61 have been amended, claims 56 and 58 have been canceled, and claims 65-71 have been added. Claims 1-55, 57 and 59-71 are pending in the application, with claims 1, 14, 22, 23, 27, 52, 53, 57 and 62 being the independent claims. The Examiner has withdrawn claims 24, 25 and 29 from consideration.

Support for the amendment of claims 1, 14, 52 and 57 is found in the specification at page 43, line 29. Alternative language is proposed in claims 53 and 61. Support for new claim 65 is found in the specification at page 48, last line to page 49, line 19. Support for new claim 66 is found in the specification at page 14, lines 23-24 and 28-30; and page 19, lines 7-8. Support for new claims 67-70 is found in the specification at page 18, lines 31-33; page 40, lines 26-27; and page 43, lines 16-18. Support for new claim 71 is found in the specification at page 29, lines 26-27; and page 59, lines 19-32.

No new matter has been added by these amendments.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

Rejection Under 35 U.S.C. § 103

In the present Office Action at pages 3-5, the Examiner has rejected claims 1-18, 21, 22, 23, 26-28 and 30-36 under 35 U.S.C. § 103(a) as allegedly being obvious over Rewinkel *et al.*, *Curr. Pharm. Design* 5:1043-1075 (1999) (hereinafter "Rewinkel"), in

view of de Nanteuil *et al.*, U.S. Patent No. 5,814,622 (hereinafter "de Nanteuil") and in further view of Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams"). Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established.

Briefly, the Examiner asserts (1) that Rewinkel discloses a boronic acid having a methoxyalkyl substituent for R9 in present claim 1, a proline as recited in claim 17, a hydrophobic moiety in the form of a diphenylalanine residue, and a protected N-terminal amine group, along with a Ki for thrombin inhibition of 14 nM which is below 100 nM as recited in present claims 7 and 28; (2) that de Nanteuil discloses organoboronic acids and pharmaceutically acceptable salts thereof; and (3) that Adams discloses that pharmaceutically acceptable salts of organoboronic acids include alkaline metal salts, alkaline earth metal salts, and amino salts. Therefore, according to the Examiner, it would have been *prima facie* obvious for one of ordinary skill to have taken the organoboronic acid compounds of Rewinkel, and modify them in view of the disclosure of Adams by creating pharmaceutically acceptable salts thereof to produce the presently claimed compounds and compositions. Applicants respectfully disagree with these conclusions and the reasoning upon which they are based.

At page 5 of the Office Action, the Examiner stated:

> [C]hoosing salts of a pharmaceutically active compound in order to improve the properties such as stability, hydroscopicity [sic] and flowability of the said compound is well within purview [sic] of one of ordinary skill in the art. Applicants' arguments that the boronic acids are known to be unstable provides further motivation for one of ordinary skill in the art to form a salt of the said acid.

Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element of the claimed invention. Additionally, one of ordinary skill in the art must have a reasonable expectation of success in obtaining the claimed invention and that it will work for its intended purpose. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); M.P.E.P. § 2143.02. Here, the prior art fails to provide a reasonable expectation of success. The claimed compounds are therapeutic thrombin inhibitors. Given the state of the art prior to Applicants' invention, it would have at best been obvious to try to make the claimed base addition salts of peptidyl boronic acids, but it would not have been predictable that a base addition salt of a peptidyl boronic acid would be stable enough to be useful in a therapeutic formulation.

In the Office Action, the Examiner cited *In re Williams*, 89 USPQ 396 (CCPA 1951) for the proposition that it would have been "obvious to form salts from known acids." *See* the present Office Action at page 4, first paragraph. Applicants respectfully disagree. In *Williams*, the issue was whether it was obvious to make a salt of pantothenic acid, which is a carboxylic acid. In relying on *Williams*, the Examiner appears to assume that peptidyl organoboronic acid compounds behave the same as carboxylic acids, such that it would purportedly be reasonable to expect that a base addition salt of a peptidyl boronic acid would exhibit improved qualities, relative to the free boronic acid. If that is the Examiner's assumption, it is an incorrect assumption, because knowledge of how a salt of a carboxylic acid behaves would not predict how a salt of a peptidyl boronic acid would behave. Furthermore, as will be discussed below, the prior art, as a whole, would have led one of ordinary skill in the art away from making a base addition salt of a peptidyl boronic acid.

The Examiner also relies on Davies *et al.*, *Pharm. J. 266:*322-323 (2001) (hereinafter "Davies") at page 4 of the Office Action. However, Davies actually supports Applicants' position that salts of peptidyl boronic acids would not have been obvious. Davies provides that "[t]here is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct." Davies at page 322, column 1, second paragraph. As Davies explains, "[w]hen a drug is formulated as a salt, the particular salt form determines the physiochemical properties of the product: stability, solubility and dissolution." Davies at page 322, column 1, third paragraph. However, the properties of a salt are not predictable, because "[a] decision to change the salt form at a later stage introduces the need to repeat toxicological, formulation, and stability tests . . . ." Davies at page 322, column 1, fourth paragraph.

At page 323, middle column, Davies discusses stability further, and explains that "[s]alts of mineral acids such as hydrochlorides, sulphates and methane sulphonates are highly polar," which leads to hygroscopicity, which can reduce stability, particularly if the drug is susceptible to hydrolytic degradation, as is the case with boronic acids. Thus, forming some salts of a boronic acid would be expected to reduce solubility, and thus reduce the value of the salt as a thrombin inhibitor.

Preparing a salt of an active ingredient, such as a peptidyl boronic acid, is an unpredictable endeavor. One would not reasonably expect that a particular cation would form a salt with a peptidyl boronic acid that would be useful as a thrombin inhibitor. For a compound to be useful as a thrombin inhibitor, it must stable enough to be stored.

However boronic acids are notoriously unstable. International Patent Application Publication No. WO 02/059130 (hereinafter "*Gupta*"; of record in the present application) discloses that alkylboronic acids are relatively difficult to obtain in analytically pure form, that they readily form boroxines (anhydrides) under dehydrating conditions, and that they are often air-sensitive, *e.g.*, to oxidation, and concludes that "[t]hese difficulties limit the pharmaceutical utility of boronic acid compounds." Gupta at ¶ [0004]. Moreover, Wu *et al.*, *J. Pharm. Sci.*, *89*: 758-65 (2000) (hereinafter "*Wu*"; of record in the present application) discloses that 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$ exhibited erratic stability behavior and was quite unstable in certain solvents. Wu at page 758, right column.[1]

Aware of the instability of boronic acids and of the "erratic stability behavior" of organoboronates such as a peptide boronic acid during attempts to formulate it for pharmaceutical uses, a person of ordinary skill, upon reading the references, would have been led away from trying to make a salt of a peptidyl boronic acid for use as a thrombin inhibitor. For example, Gupta did not make a salt, but instead solved the stability problem by formulating the boronic acid as a lyophilizate with another compound, *e.g.*, a sugar, which lyophilizate can be reconstituted with an aqueous solvent such as saline for administration. The lyophilizate was found to produce a mass spectrum signal indicative of the formation of a "covalent ester adduct." Gupta at ¶¶ [0136], [0141], the ester adduct being illustrated at ¶ [0070].

[1] At page 22 of the Amendment and Reply filed in the present application on March 20, 2007, Applicants discussed V. Martichonok and J.B. Jones, *J. Am. Chem. Soc.*, **1996**, *118*, 950-58 (hereinafter "*Martichonok*"). Applicants pointed to Martichonok at page 951, right-hand column, and explained that in Martichonok, the authors made a diethanolamine ester to impart stability to boronic acids. Applicants now realize that Martichonok referred to diethanolamine derivatives, not to an ester, and Applicants respectfully wish to correct the record.

Indeed, in making this rejection by relying in part on the disclosure of Adams, the Examiner apparently believes that Adams would have motivated one of ordinary skill to make salts of organoboronic acids. This conclusion is not supported in Adams, since Adams relates to the boronic acid drug bortezomib (Velcade®) -- compound MG-341 on cols 59-60 of Adams -- and yet it was found that stabilization of Velcade® required *esterification* of the organoboronate, as indicated in Wu and Gupta (*see also* the package insert for Velcade® filed in the present application on March 20, 2007, which confirms that this compound is marketed as a mannitol *ester*).

Furthermore, Applicants have conducted stability testing of one embodiment (referred to as "TRI 50c") of the presently claimed compound, in the free acid and sodium salt forms. A summary of the results of a stability study of the free acid was filed in the present application on March 20, 2007. What these data show is that there was significant morphological degradation observed in the free acid form of this compound over time, as depicted in Table 1 and Figure 7.1 of the stability report. Moreover, Table 2 of the stability report shows that at 25°C and 60% relative humidity for three months, the moisture content nearly doubled, from 3.96% w/w to 7.66% w/w. Furthermore, table 3 shows that after three months, the purity decreased from 97.18% to 58.83%. These results confirm the observations reported in Examples 27 and 28 of the present application, and the calcium salt stability data reported in the first Table of Example 13 of commonly owned U.S. Patent No. 7,112,572.

Hence, in view of the cited references and information that was readily available in the art at the time, instead of being motivated to make the boronic acid salts of the presently claimed invention, one of ordinary skill would more likely have been taught

away from making such revisions to the compounds disclosed in Rewinkel. That is, aware of both the problem with stability of boronic acids and two reported solutions to the problem, a person of ordinary skill in the art would not have been motivated to make the presently claimed invention but instead would have pursued one of the aforementioned solutions, *i.e.*, lyophilization or esterification.

At page 5 of the Office Action, the Examiner argued that Applicants' showing of unexpected results is not commensurate in scope with the claimed invention. Applicants respectfully disagree. Applicants have shown that the sodium, calcium and lysine salts confer increased stability for Tri 50c. Moreover, it is Applicants' position that, absent a reasonable expectation of success, the claimed invention would not have been *prima facie* obvious.

For at least the foregoing reasons, the cited references do not render claims 1-18, 21, 22, 23 26-28 and 30-36 *prima facie* obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Double Patenting

The Examiner has rejected claims 1-23, 26-28 and 30-64 for non-statutory obviousness-type double patenting over claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572. Applicants respectfully request that this rejection be held in abeyance until the Examiner has identified allowable subject matter in the present application. At such time, Applicants will consider filing a terminal disclaimer to obviate this rejection.

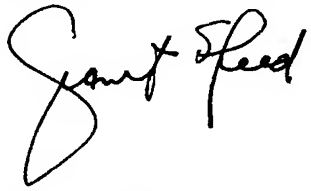
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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